reducing HLH related immunopathology, this strategy leads to profound iatrogenic marrow and immune suppression, thus greatly increasing the risk of opportunistic infection. With the explosion of cinically available immunosuppressive agents, there is a critical need to define which sorts of immune suppression offer the most effective yet focused treatment for HLH.

In this study, we utilize our animal model of HLH as a preclinical screen to test the effectiveness of targeted immune suppression using agents that interfere with interleukin-2 production or signal transduction in T cells. LCMV-infected prf-/- mice experience exaggerated symptomaticity, massive elevations in serum IFNγ, and consumptive anemia before becoming moribund. When these mice are treated with the mTOR inhibitor rapamycin, either alone or in combination with inhibitors of T cell costimulation (CTLA4-Ig or anti-CD2), they show improvements in disease severity, survival, and hemoglobin levels similar to the benefit seen in animals treated with etoposide monotherapy. We will present data showing the effects of these agents on the activation of dendritic cells, T cells, and macrophages in the context of our animal model.

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OUTCOMES AFTER ADDITION OF RABBIT-ATG TO THE STANDARD BU + CY PREPARATIVE REGIMEN FOR ALLOGENEIC MATCHED SIBLING DONOR (MSD) HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR HEMOGLOBINOPATHIES IN CHILDREN

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Introduction: Allogeneic HSCT for hemoglobinopathies following myeloablative conditioning in MSD setting results in excellent outcomes in children (85-95% 5 year EFS). Though outcomes are encouraging, there is still a 7%-10% incidence of graft rejection and 15-20% incidence of GVHD. We proposed the hypotheses, that administration of 10 mg/kg dose of rabbit-ATG (Thymoglobulin, Genzyme, Cambridge, USA) during the peri-transplant period for MSD HSCT, will lead to partial in-vivo T-cell depletion; eliminating the risk of rejection and GVHD while not increasing the risk of infections.

Methods: Patients with sickle cell disease (SCD) with sequelae and transfusion dependent β-thalassemia, underwent MSD HSCT on an IRB approved study starting Jan, 2003. All patients received iv Busulfan (16 mg/kg over 4 days; targeted AUC of 900-1350 μM/mt, based on 1st dose PK); Cyclophosphamide (50 mg/kg × 4 days) and r-ATG (2.5 mg/kg/day from days -6 to -3). Cyclosporine and standard short course Methotrexate on days +1, +3 and +6 was given for GVHD prophylaxis.

Results: 11 patients (9 SCD and 2 β-Thalassemia; 6 females and 5 males) have received the preparative regimen. Median age of patients' was 4 years (range,18 months-18 years). The r-ATG infusions were well tolerated with no missed doses. All patients received sibling BM grafts with the median cell dose of 3.5×10^8 TNC/kg (range, 1.8-10.1×10^8 TNC/kg). All patients developed grade II-III mucositis. One patient developed mild VOD and one patient had seizures associated with reversible posterior leuco-encephalopathy syndrome. All patients engrafted (ANC $>0.5 \times 10^9$/L) by median of day +15 (range, day +10 to +23). 2 patients developed CMV reactivations that responded to treatment. No other viral reactivations or fungal infections were detected. Serial chimerism analysis post-HSCT shows stable donor engraftment in all patients. There was no TRM and none of the patients developed acute GVHD. One patient developed limited chronic GVHD of the skin. EFS is 100% after a median follow up of 404 days (range, 61-2409 days) with complete resolution of underlying disease. End organ function is stable and immune reconstitution is complete in all the patients evaluable >1 year post-HSCT.

Conclusions: Addition of 10 mg/kg dose of rabbit-ATG to the standard Bu + CY myeloablative regimen has minimized the incidence of rejection, acute and chronic GVHD without increasing toxicity or incidence of infections for MSD HSCT for hemoglobinopathies.

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OUTCOME OF UNRELATED DONOR BLOOD AND MARROW TRANSPLANTATION (BMT) FOR CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN THIRD REMISSION

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Although BMT plays an important role in the therapy of ALL, the outcome of children transplanted in third remission (CR3) is poorly defined. We reviewed 155 children, median age 11 years (range, 1-18), who received an unrelated donor BMT for ALL in CR3 from 1990 to 2005. Median time from diagnosis to first relapse was 35 months, and median time from first to second relapse was 26 months (range, 4-116). Stem cell sources were bone marrow (n = 115), peripheral blood stem cells, PBSC (n = 11) or cord blood (n = 29). BM and PBSC donor-recipient pairs (n = 126) were matched at HLA-A, B, C and DRB1 (n = 40, 32%), or mismatched at either one locus (n = 36, 28%) or ≥ 2 loci (n = 50, 40%). Cord blood donor-recipient pairs (n = 29) were matched at HLA-A, B, DRB1 (n = 1) or mismatched at either one locus (n = 6) or 2 loci (n = 22). 92% of patients received total-body irradiation (TBI) and 42% received TBI dose >1300 cGy. Graft vs. host disease (GVHD) prophylaxis was cyclosporine or tacrolimus plus another agent in 63% of patients. 31% of patients received T-cell depleted BM grafts and 52% received ATG as part of transplant conditioning regimen. The cumulative incidence of neutrophil recovery was 95% (95% CI, 95- 98%). The day-100 cumulative incidence of grade 2-4 acute GVHD was 58% (50-66%) and chronic GVHD at 3-years, 28% (95% CI 21-35%). The risk of chronic GVHD higher in PBSC recipients (RR 2.85, 95% CI1.18-6.92, p = 0.01). The incidence of non-relapse mortality (NRM) was 19% (95% CI 14-26%) at 100 days, 41% (95% CI 33-49%) at 1-year and 45% (95% CI 37-53%) at 5-years. Causes of NRM included graft failure (2%), GVHD (5%), infection (12%), organ toxicity (21%), secondary malignancies (3%) and other causes (6%). 47 patients are alive at last follow-up, with median follow-up of 6 years. In multivariate analysis, the interval between first and second relapse was associated with relapse after BMT. Relapse risks were higher in patients for whom this interval was ≤26 months (RR 2.50, 95% CI 1.28-4.76, p = 0.01). No risk factors were identified for non-relapse mortality. The 5-year cumulative incidence of relapse was 17% (95% CI 9-26%) and 34% (95% CI 24-45%) in patients with a second relapse >26 months and ≤26 months from their first relapse, respectively. Corresponding 5-year leukemia-free survival rates were 33% (95% CI 23-44%) and 26% (95% CI 16-36%). Unrelated donor BMT results in acceptable disease free-survival in children with ALL in CR3, especially those experiencing a late second relapse.

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REDUCED INTENSITY CONDITIONING (RIC) WITH FLU-BU-ATG AND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FROM HLA IDENTICAL DONORS: RELAPSE-FREE SURVIVAL (RFS) OF 42% IN PEDIATRIC PATIENTS WITH HIGH-RISK HEMATOLOGIC MALIGNANCIES

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RIC regimens prior to allogeneic HSCT diminish potential complications compared with myeloablative therapy. We report the experience of 31 RIC HSCT for children/adolescents with hematologic malignancies at high-risk for relapse or complications of full-intensity conditioning due to disease state, prior myeloablative HSCT and/or co-morbid conditions. The RIC regimen was comprised of fludarabine, 180 mg/m2 over 6 days, 2 days of IV busulfan; and 4 days of ATG (equine or rabbit). Diagnoses included: ALL (14, ≥CR3 in 7), AML (5), treatment-related myelodysplastic

syndrome/secondary AML (5), Non-Hodgkin's Lymphoma (4), or CML (3). There were 22 males, 9 females, ages 2 – 17 yrs, median 11. Ten patients (pts) had previously undergone myeloablative therapy and HSCT, 8 pts had comorbid conditions increasing their risk for treatment failure. Stem cell sources included 16 unrelated donors (URD), 13 matched sibs and 2 mis-matched relatives. 29 of 31 HSC donations were from mobilized peripheral blood and 2 were marrow. Graft-versus-host disease (GVHD) prophylaxis was cyclosporine A (CsA) alone in 9 pts and CsA and mycophenolate in 22 pts. Median time to an ANC >500/mcl was 18 days and unsupported platelet count >20,000/mcl was (28 pts) 17 days, 7 pts required no platelet support. One pt failed to engraft and 3 had secondary graft loss. 6 pts developed Grade III-IV acute GVHD, 14 of the 24 pts surviving more than 100 days developed chronic GVHD (8 limited, 6 extensive). 16 pts survive, 10 without disease relapse or progression. 100-day mortality (7 of 31, 23%) was from infection (3), GVHD (3) and relapse (1). 8 of 19 pts with matched donors relapsed, 2 died of infections complicating GVHD whereas 3 of 12 pts with mismatched donors relapsed, 7 died of complications: infection, GVHD or graft failure.

RFS for patients HLA-matched at the allele (8 of 8) level was 42% vs 18% ($p = 0.04$) with ≥ 1 mismatch while Overall Survival was 64% vs 24% ($p = 0.02$). Our results suggest RIC allogeneic HSCT should be considered for pediatric pts with hematologic malignancies, especially if a well-matched (related or unrelated) donor can be identified. Our current studies are focused on reducing the toxicity for recipients of mismatched grafts.

Patient Characteristics (n = 31)	
Age—yrs, (median, std dev)	11 +/- 4
M – F	22 – 9
Prior Autologous HSCT	6
Prior Allogeneic HSCT	4
Matched Sib HSC	13
URD or mm Relative HSC	18
HSC Dose–CD34+ cells/kg, x10e6 (median, std dev)	8.8 +/- 5.7

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OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) IN CHILDREN WITH CONGENITAL HEART DISEASE (CHD)

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CHD is the most common birth defect in the US. Improved supportive care has resulted in more pediatric and adult survivors who may develop indications for HSCT. We hypothesized there would be overrepresentation of CHD in children undergoing HSCT, as several inherited immune and bone marrow (BM) failure disorders are associated with an increased CHD prevalence. As HSCT outcomes of patients (pts) with CHD are not well known, we conducted a retrospective chart review of 1185 sequential HSCT on 1031 pts performed at Children's Hospital Boston from 1989-2007. We found 10 pts with major cardiac structural defects requiring surgical catheterization or intervention for repair or palliation. Cardiac characteristics are outlined in the table. 8 pts underwent allogeneic HSCT for ALL (n = 4), AML (n = 1), CML (n = 1), Diamond-Blackfan anemia (n = 1), and DiGeorge syndrome (n = 1) using BM from matched sibling (n = 4) or unrelated donors (n = 3). 1 pt received fresh T cells from a haploidentical donor. 2 pts underwent autologous HSCT using BM for ALL (n = 1) and AML (n = 1). Conditioning was cyclophosphamide (CY) and TBI +/- other chemotherapy (n = 7) or CY +/- other chemotherapy (n = 2). The haploidentical HSCT was performed without conditioning. GVHD prophylaxis was cyclosporine and methotrexate, plus corticosteroids for some unrelated BM recipients. Median time to absolute neutrophil count of 500/uL was 25 days (D, range 17-50). 2/8 allogeneic HSCT recipients developed acute GVHD (1 Grade 2, 1 Grade 3). 1 received systemic corticosteroids. 50% of pts developed febrile neutropenia. 2 had documented bacteremia, but no endocarditis or life-threatening infectious toxicity was seen. Combined rates of grade 3, 4, and 5 cardiac, pulmonary, and renal toxicities (NIH CTC v. 3) through D + 100 were 10%, 10%, and 0%, respectively. No pts died in the first 100 D post-HSCT. Pt follow-up ranged 0.44-9.25 yrs (median 3.9yrs). 5 pts died at a median of 690D (range 159-780) of relapse (n = 4) and pulmonary hemorrhage (n = 1). 5 pts underwent post-HSCT cardiac repair. 4 procedures were completed uneventfully; 1 pt died of sepsis and pulmonary hemorrhage. Overall CHD rates were 2-5 × greater in our pts than US rates. We found promising acute and long-term HSCT outcomes for children with CHD, who readily tolerated HSCT associated volume challenges, febrile neutropenia, and regimen-related toxicity, and suggest that children with CHD should not be excluded from HSCT solely due to their cardiac anomalies.

Cardiac Status on Admission

Patient	Age at Transplant	Cardiac Diagnosis	Prior Surgery	Prior Anthracycline	Chronic Cardiac Rx
1	2.5	Complex single right ventricle	Bidirectional Glenn shunt	No	Enalapril, aspirin
2	5.3	Coarctation, patent ductus arteriosus	None	Doxorubicin 60 mg/m^2 + dexrazoxane	None
3	8.9	Truncus Arteriosus Type 1A, ventricular septal defect	Truncus repair	No	Enalapril
4	13.9	Atrial septal defect	None	Daunorubicin 135 mg/m^2	None
5	0.3	Tetralogy of Fallot	Tetralogy of Fallot repair	No	Digoxin
6	8	Pulmonary stenosis	Pulmonary balloon valvuloplasty	Doxorubicin 60 mg/m^2	None
7	10.6	Atrioventricular canal defect	Atrioventricular canal defect repair	Doxorubicin*	None
8	18.5	Primum atrial septal defect, cleft mitral valve	None	Daunorubicin 135 mg/m^2	None
9	1.5	Bicommissural aortic valve, coarctation, mitral stenosis, ventricular septal defect	None	Daunorubicin 128 mg/m^2; Idarubicin 30.6 mg/m^2	None
10	6.3	D-loop transposition of the great arteries, ventricular septal defect, pulmonary stenosis	Blalock-Taussig shunt, Rastelli procedure, conduit revision, pulmonary valve replacement	Doxorubicin 60 mg/m^2 + dexrazoxane	Aspirin

*Initial care at outside institution, cannot confirm dose.

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RISK ADAPTED ALLOGENEIC STEM CELL TRANSPLANTATION (ALLOSCT) FOR ACQUIRED SEVERE APLASTIC ANEMIA (SAA) IN PEDIATRIC RECIPIENTS: IMPROVED OUTCOMES WITH UNRELATED DONORS

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Background: AlloSCT from matched sibling donors (MSD) has resulted in the highest survival rates in children and adolescents with